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| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/809,753 | GELFAND ET AL. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-10,12-14,20-30,38-40 and 42-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12-14,20-30,38-40 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1, 3-10, 12-14, 20-30, 38-40, and 42-47 are pending.

2. The following new grounds of rejections are necessitated by the amendment filed 10/20/04.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-10, 12-14, 20-30, 38-40, and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of inhibiting allergen induced airway hypreresponsiveness by administering human CGRP alpha wherein the human CGRP alpha inhibits OVA-induced airway hyperresponsiveness to methacholine, **does not** reasonably provide enablement for a method to inhibit allergen-induced airway hyperresponsiveness in *all* mammal comprising administering to said mammal any calcitonin gene related peptide (CGRP), any "fragment of any CGRP" that is an agonist of any CGRP wherein the fragment binds to and activates any CGRP receptor, any "homologue" of any CGRP that is an agonist of any CGRP, wherein the homologue binds to and activates any CGRP receptor, any "fragment of CGRP" that is an agonist of CGRP wherein the fragment has "substantially the same or increased biological activity as compared to any naturally occurring CGRP peptide", any "homologues of CGRP" that is any agonist of CGRP wherein the homolog has "substantially the same or increased biological activity as compared to any naturally occurring CGRP peptide" as set forth in claims 1, 3-10, 12-14, 20-30, 38-40, and 42-47 in conjunction with *any* "CGRP receptor activity modified protein (RAMP)" in claim 28 or *any* other β-agonists (long or short acting), *any* leukotriene modifiers such as any (inhibitors or receptor antagonist), or *any* "phosphodiesterase inhibitors" as set forth in claim 27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of inhibiting allergen induced airway hypreresponsiveness by administering human CGRP alpha wherein the human CGRP alpha inhibits OVA-induced airway hyperresponsiveness to methacholine (page 61, in particular). In contrast, treatment of mice with CGRP antagonist (8-37), at 2 hr prior to each allergen challenge, did not produce any significant change in the extent of measured AHR (Figs. 3A and 3B). The specification defines the term "CGRP receptor agonist" on page 25 as any compound (agent), including but *not limited to* antibody, CGRP, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

The specification does not teach how to make any fragment of any CGRP fragment and any homolog of any CGRP that binds to and activates any CGRP receptor without the amino acid sequence, much less for use in inhibiting allergen-induced airway hyperresponsiveness in all mammal. There is insufficient guidance as to which amino acid within the full length of all CGRP can be deleted, substituted, or modified, and that the resulting fragment and homolog of any GCRP has agonist activity, let alone the CGRP fragment and homolog bind to which CGRP receptor, in turn, effective for treating allergen-induced airway hypreresponsiveness. The terms "homolog", "fragment" and "CGRP" without the amino acid sequence have no structure. Further, the "homologue" as defined in instant specification is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is insufficient guidance as to which amino acids within all GCRP to be added, deleted, substitute for which amino acids and whether the resulting CGRP homologue maintains the same function as CGRP, in turn, would be useful for inhibit airway hyperresponsiveness sensitized by allergen.

Dakhama et al teach there are two isoforms of calcitonin gene-related peptide (α-CGRP and β-CGRP) (see page 215, col. 2, in particular) and there are two CGRP receptors in human have been identified (see page 216, col. 1, in particular). Dakhama et al teach CGRP is not a brochoconstrictor of either human or animal airways and is not a mediator of neurogenic inflammation. Dakhama et al teach administering CGRP receptor antagonist CGRP8-37 to sensitized mice either during or after completion of allergen airway challenge to inhaled methacholine did not inhibit development of AHR or airway inflammation in these animals (See page 218, col. 1, last paragraph, in particular). Dakhama et al teach whether the function of CGRP has some bronchoprotective and anti-inflammatory properties prevails in vivo and under which circumstances remain to be fully established given the wide distribution of CGRP and its receptors to multiple organs and cellular targets. At best, the complete physiological functions are far from being established and the complete structural and biochemical characterization of CGRP receptor subtypes are necessary for development of highly selective pharmacological agent such as CGRP agonist (see page 218, col. 2, Conclusion, in particular).

Further, the specification does not define the term "substantially the same or increased biological activity" as recited in claim 47. Given the CGRP peptide has different biological activity on different cell and tissue as taught by Dakhama et al, there is insufficient guidance as to which biological activity should the fragment be measured against. Further, the term "substantially the same" is not defined in the specification. A 50% difference in biological activity would still be substantially the same.

Kanazawa *et al*, of record, teach a CGRP fragment such as CGRP8-37. Although the reference CGRP fragment binds to the CGRP receptor, it has antagonistic activity to CGRP (see abstract, in particular). Kanazawa et al further teach CGRP homolog such as adrenomedullin (AM) that has 50% sequence identity to CGRP. While the reference CGRP homolog inhibits histamine induced bronchoconstriction in a dose dependent manner, the CGRP or the CGRP fragment CGRP8-37 alone did not affect pulmonary resistance. Further, pretreatment with CGRP or the CGRP fragment CGRP8-37 did not significantly affect histamine-induced bronchoconstriction (See abstract, in particular). Given the unlimited number of undisclosed "homolog", and "CGRP fragment" that bind to more than one CGRP receptors in all mammal, there is insufficient in vivo working example demonstrating that all CGRP fragment, all homologue and all CGRP are effective for the claimed method of inhibiting allergen-induced airway hyperresponsiveness.

Whitehead et al teach allergen induced airway hyperresponsiveness is mouse strain dependent (see entire document, abstract, in particular). It is not clear that the reliance on one strain of mice accurately reflects the efficacy of the breadth to inhibit allergen-induced airway hypreresponsiveness in *all* mammal as encompassed by the claims.

Other than human CGRP, it is unpredictable which undisclosed "homolog", and "CGRP fragment" are effective for inhibiting allergen induced airway hyperresponsiveness. Until the specific homolog, CGRP fragment, and GCRP mimetic have been identified and have the specific agonist activity, it is unpredictable which CGRP fragment, and homologue of CGRP is effective for inhibiting allergen-induced airway hyperresponsiveness in which mammal who have allergen induced airway hyperresponsiveness or which mammal at risk of developing allergen-induced airway hypreresponsiveness. The specification does not teach how to predict who is at risk of developing allergen-induced airway hypreresponsiveness among all mammal. As such, the disclosure merely invites one of skill in the art for further experimentation.

With regard to "CGRP receptor activity modified protein (RAMP)" in claim 28 and *any* other β-agonists (long or short acting), *any* leukotriene modifiers such as any (inhibitors or receptor antagonist), or *any* "phosphodiesterase inhibitors" as set forth in claim 27, in addition to the problem of CGRP fragment and CGRP homolog in the claimed method, the term "CGRP receptor activity modified protein" without the amino acid sequence has no structure. The terms "β-agonists", "leukotriene modifiers" and "phosphodiesterase inhibitors" without the chemical structure have no structure, let alone how to make and use such as compound in the claimed method.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Given the unlimited number of "CGRP receptor activity modified protein (RAMP)", "β-agonists", "leukotriene modifiers" and

"phosphodiesterase inhibitors" and the lack of sufficient in vivo working example, it is unpredictable which undisclosed "CGRP receptor activity modified protein (RAMP)", "β-agonists", "leukotriene modifiers" and "phosphodiesterase inhibitors" in conjunction with which CGRP, CGRP fragment or CGRP homolog is efficacious for a method to inhibit allergen-induced airway hyperresponsiveness in all mammal.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended to recite fragment of CGRP that is an agonist of CGRP, wherein the fragment binds to and activates a CGRP receptor and a homologue of CGRP that is an agonist of CGRP, wherein the homologue binds to and activates a CGRP receptor. (2) applicants submit that the specification and the art provide sufficient guidance to one of skill in the art to readily make and use the recited homologues and peptides without undue experimentation.

In contrast to applicants' assertion that the specification and the art provide sufficient guidance to one of skill in the art to readily make and use the recited homologues and peptides without undue experimentation, The specification does not teach how to make any fragment of any CGRP fragment and any homolog of any CGRP that binds to and activates any CGRP receptor without the amino acid sequence, much less for use in inhibiting allergen-induced airway hyperresponsiveness in all mammal. There is insufficient guidance as to which amino acid within the full length of all CGRP can be deleted, substituted, or modified, and that the resulting fragment and homolog of any GCRP has agonist activity, let alone the CGRP fragment and homolog bind to which CGRP receptor, in turn, effective for treating allergen-induced airway hypreresponsiveness. The terms "homolog", "fragment" and "CGRP" without the amino acid sequence have no structure. Further, the "homologue" as defined in instant specification is

referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is insufficient guidance as to which amino acids within all GCRP to be added, deleted, substitute for which amino acids and whether the resulting CGRP homologue maintains the same function as CGRP, in turn, would be useful for inhibit airway hyperresponsiveness sensitized by allergen.

In fact, the enclosed evidentiary reference Dakhama et al teach there are two isoforms of calcitonin gene-related peptide (α-CGRP and β-CGRP) (see page 215, col. 2, in particular) and there are two CGRP receptors have been identified (see page 216, col. 1, in particular). Dakhama et al teach CGRP is not a brochoconstrictor of either human or animal airways and is not a mediator of neurogenic inflammation. Dakhama et al teach administering CGRP receptor antagonist CGRP8-37 to sensitized mice either during or after completion of allergen airway challenge to inhaled methacholine did not inhibit development of AHR or airway inflammation in these animals, clearly indicating that endogenous CGRP is not a mediator of AHR (See page 218, col. 1, last paragraph, in particular). Dakhama et al teach whether the function of CGRP as bronchoprotective and anti-inflammatory agent prevails in vivo and under which circumstances remain to be fully established given the wide distribution of CGRP and its receptors to multiple organs and cellular targets. At best, the complete physiological functions are far from being established and the complete structural and biochemical characterization of CGRP receptor subtypes are necessary for development of highly selective pharmacological agent such as CGRP agonist (see page 218, col. 2, Conclusion, in particular).

Other than human CGRP, it is unpredictable which undisclosed "homolog", and "CGRP fragment" are effective for inhibiting allergen induced airway hyperresponsiveness. Until the specific homolog, CGRP fragment, and mimetic have been identified and have the specific agonist activity, it is unpredictable which CGRP fragment, and homologue of CGRP is effective for inhibiting allergen-induced airway hyperresponsiveness in *all* mammal who have allergen induced airway hyperresponsiveness or at risk of developing allergen-induced airway hypreresponsiveness. The specification does not teach how to predict who is at risk of developing allergen-induced airway hypreresponsiveness among all mammal. As such, the disclosure merely invites one of skill in the art for further experimentation.

5. Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "...provoking agent that causes a 20% fall in FEV1 ($PC_{20}FEV_1$) wherein said concentration is less than...mammal;" in Claim 46 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 10/25/04 do not provide a clear support for the said phrase. In fact, the specification on page 14, line 4-6 discloses that "in human, the does or concentration of provoking agent (i.e. methacholine or histamine) that causes a 20% fall in FEV1 ($PC_{20}FEV_1$) is indicative of the degree of AHR. The specification on page 15 discloses when Mch is used as a provoking agent; the degree of AHR is defined by the provocative concentration of Mch needed to cause a 20% drop of the FEV1 of a mammal.

The "...substantially the same or increased biological activity..." in claim 47 has no support in the specification as filed. The passage pointed out by applicant does not have support for said phrase.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, 42-43, and 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) as evident by Beaupre et al (Thorax 36(10): 731-6, Oct 1981; PTO 892).

Cadieux *et al* teach a method of inhibiting allergen induced airway hyperresponsiveness in a mammal comprising administering to a mammal such as guinea pigs a CGRP agent such as calcitonin gene related peptide (CGRP) wherein the reference mammal has been sensitized to an allergen such as ovalbumin (See entire document, Methods, Figure 2, page 237, column 2, page 241, column 2, third paragraph, in particular). The reference agent is administered at a dose of 0.38 μg/ kg body weights, which is about 0.1 to about 20 μg/kg body weight (See page 237, column 1, 5$^{th}$ paragraph, in particular). Cadieux *et al* teach that pretreatment of CGRP at various

concentrations such as $10^{-9}$ to $10^{-6}$ M, which is about 0.1 μg/ kg body weight to about 10 or 5 about μg/ kg body weight of the reference mammal (See page 238, column 2, 1st paragraph, in particular). The term "about" expands the claimed range to include the reference concentration. The reference CGRP inherently binds to and activates a CGRP receptor in the lungs of the reference mammal. Claims 5 and 8-9 are included in this rejection because the reference teaches administering CGRP five minutes prior challenge and this step is repeated, and five minutes is within 12 hours, 2 hours or between 48 hours or less prior to exposure to AHR provoking stimulus. Claim 25 is included in this rejection because the reduction of airway hyperresponsiveness such that the FEV1 value is improved by at least about 5% is inherent properties of the reference CGRP and properties of CGRP cannot be separate from the compound. The reference agent is targeted to cells in the lung such as smooth muscle cells and epithelial cells (See page 241, column 1, line 2nd paragraph, in particular). The reference agent is administered by intravenous injection or by direct delivery to the lung in the organ bath of the reference mammal (See Chemicals and Solutions, caption of Figure 2, page 236, column 2, 2nd paragraph, in particular). Cadieux et al teach in vivo measurement of airway responses in guinea pigs sensitized with ovalbumin (page 236, animals and Sensitization procedures, in particular) and sensitivity to provoking agent such as acetylcholine or SP is measured with or without OA-sensitization and CGRP treatment (see page 236, col. 2, in particular). At highest dose of CGRP 6-M, CGRP inhibits OA-sensitized guinea pig bronchus (7.2 ± 4.5) airway hyperresponsiveness to SP as compared to control (20.3 ± 1.5) and is statistically significance ($p< 0.05$ versus control). The reference CGRP inherently binds to and activates a CGRP receptor in the lung of the reference mammal since it is used to inhibit airway hyperresponsiveness. Claims 43 and 45 are included in this rejection because it is within the purview of one ordinary skill in the pharmaceutical art to compared to control not treated with CGRP in order to arrive at the statistically significance of $P<0.05$ as taught by Cadieux et al (see Figure 2 on page 237, in particular). The recitation of provoking agent that causes a 20% fall in FEV1(PC20FEV1) wherein said concentration is less than the concentration required to cause a 20% fall in FEV1(PC20FEV1) in non-allergen-sensitized animal is within the teachings of Cadieux et al who teach in vivo measurement of airway responses in guinea pigs sensitized with ovalbumin (page 236, animals and Sensitization procedures, in particular) and sensitivity to provoking agent such as acetylcholine or SP is measured after OA-sensitization and CGRP treatment (see page 236, col. 2, in particular). The evidentiary reference Beaupre et al teach that PC20FEV1 is the

concentration of provoking agent such as histamine that causes a 20% fall in FEV1 and PC20FEV1 is a more helpful index in characterizing the clinical state of asthmatic (see abstract, in particular). In fact, the instant specification discloses a variety of provoking agents such as histamine, acetylcholine are useful in measuring AHR values (see page 14, last paragraph of instant specification) and FEV1 and FVC values can be measured using methods known to those of skill in the art (see page 14, line 4-8, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that the experimental model of Cadieux et al, whether performed in non-sensitized or OVA-sensitized guinea pigs, measures only the effect of CGRP on substance P (SP) induced AHR, SP is a known sensory neuropeptide, potently induces bronchoconstriction in both non-sensitized and sensitized animals and therefore is not useful for distinguishing between other effects on the animal, such as allergen sensitization. Cadieux et al cannot measure the effect of any agent on OA-treatment, and thus the animals were selected to have the same response to SP, regardless of the OA-treatment. There is no control that shows what effect of the OA-sensitization had on AHR, because SP includes broncho constriction in all guinea pigs.
In contrast to applicants' assertion that there is no control that shows what effect of the OA-sensitization had on AHR, because SP includes broncho constriction in all guinea pigs, Table 1 on page 239 show that there is control (without OA-sensitization) treated with various concentration of CGRP (far left col of Table 1, in particular). Cadieux et al teach in vivo measurement of airway responses in guinea pigs sensitized with ovalbumin (page 236, animals and Sensitization procedures, in particular) and sensitivity to provoking agent such as acetylcholine or SP is measured after OA-sensitization and CGRP treatment (see page 236, col. 2, in particular). At highest dose of CGRP 6-M, CGRP inhibits OA-sensitized guinea pig bronchus ($7.2 \pm 4.5$) airway hyperresponsiveness to SP as compared to control ($20.3 \pm 1.5$). In fact, the instant specification discloses administration of CGRP to OA-sensitized mice and sensitivity to inhaled methacholine after OA-sensitization and CGRP treatment is measured (see Figure 3 of instant specification). Methacholine and the reference acetylcholine or SP are merely provoking agent widely used in measuring airway hyperresponsiveness (see pages 14-15 of instant specification). In fact, the instant specification discloses administration of CGRP to OA-

sensitized mice and sensitivity to inhaled methacholine after OA-sensitization and CGRP treatment is measured (see Figure 3 of instant specification).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 6-7, 10, 13-14, 22, 24, 27, 30, 40 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (or record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) as evident by Beaupre et al (Thorax 36(10): 731-6, Oct 1981; PTO 892) in view of US Pat No. 5,858,978 (of record, Jan 1999; PTO 1449) and/or US Pat No. 5,635,478 (of record, June 1997; PTO 1449).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention in claim 6 differs from the teachings of the reference only that the method wherein the agent is administered upon the detection of the first symptoms of AHR.

The claimed invention in claim 7 differs from the teachings of the references only that the method wherein the agent is administered within one hour after the detection of the first symptoms of AHR.

The claimed invention in claim 10 differs from the teachings of the reference only in that the method wherein the agent is administered every one to two days.

The claimed invention in claim 13 differs from the teachings of the reference only in that the method wherein the agent is administered at a dose of from about 0.1 μg x kilogram-1 and about 10 μg x kilogram body weight of said mammal.

The claimed invention in claim 14 differs from the teachings of the reference only in that the method wherein the agent is administered at a dose of from about 0.1 μg x kilogram-1 and about 5 μg x kilogram body weight of said mammal.

The claimed invention in claim 22 differs from the teachings of the reference only in that the method wherein the agent is administered by aerosol delivery.

The claimed invention in claim 24 differs from the teachings of the reference only in that the method wherein the agent is administered by oral delivery.

The claimed invention in claim 27 differs from the teachings of the reference only in that the method wherein the agent is administered to said mammal in conjunction with another agent such as corticosteroids (oral or injected), or phosphodiesterase inhibitor.

The claimed invention in claim 30 differs from the teachings of the reference only in that the method wherein the mammal is a human.

The claimed invention in claim 40 differs from the teachings of the reference only in that the method wherein the agent is a homologue of CGRP.

The claimed invention in claim 44 differs from the teachings of the reference only in that the method wherein the agent is human αCGRP.

The '978 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness due to constriction, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 7, lines 45-49, in particular) or administered orally such as tablet or sublingual (See column 6, lines 3-7, in particular). The '978 patent teaches the reference method is useful in treatment of a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '978 patent

teaches the reference pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 7, lines 6-61, in particular). The '978 patent teaches that the reference agents are administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 50-55, in particular) or every 24 hours or longer (See column 7, lines 35, in particular).

The '478 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 6, lines 35, in particular) or administered orally (See column 7, line 3, in particular) or administered by parenterally (See column 6, lines 37-38, in particular). The '478 patent teaches the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches the pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 6, lines 60-67 bridging column 7, lines 1-10, in particular). The '478 patent teaches the reference agents is administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 37-51, in particular). The '478 patent teaches a method of treating asthma which is a chronic airway inflammatory disease by administering human CGRP (see col. 7, line 32-34, in particular). The '478 patent teaches human CGRP are known commercially available peptides (See col. col. 2, line 37, in particular). The reference human CGRP appears to be the same human αCGRP since the term "alpha" is merely a laboratory designation to any first isolated CGRP. Claim 3 is included in this rejection because asthma induced airway hyperresponsiveness is due to inhalation or exposure to allergen. Claim 6 is included in this rejection because the references teach the reference agents are administered to ameliorate the symptoms associated with asthma. Claims 7 and 9 are included in this rejection because the '978 patent teaches administering CGRP to inhibit acute inflammation disorder such

as asthma and the recitation of administering within 1 hour after the detection of the first symptoms of AHR or administered within 2 hours or less is within the purview of one skill in the art at the time the invention was made to intervene by administering CGRP as taught by the '978 and the '478 patents.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CGRP as taught by the Cadieux *et al* for the homolog of CGRP that binds to and activate CGRP receptor or combine the CGRP as taught by Cadieux with another agent such as corticosteroids or phosphodiesterase inhibitor as taught by either the '978 patent or the '478 patent or the human αCGRP as taught by the '478 patent for a method of to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al* and the '978 patent or the '478 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '978 patent teaches that the CGRP and homologue thereof are useful for treating a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat chronic inflammatory respiratory disorders (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches human CGRP and homolog thereof are useful in treatment of a variety of acute and chronic inflammatory respiratory disorder such as asthma, by administering CGRP or homologue thereof alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, abstract, in particular). Claims 13-14 are included in this rejection because it is well within the purview of one of ordinary skill in the medicinal art to optimize doses for the particular treatment regimen. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that Cadieux et al. fail to teach a method of using CGRP to inhibit allergen-induced AHR. Applicants submit that the combination of Cadieux et al with one or both of the '978 patent or the '478 patent do not remedy the deficiencies of Cadieux et al. alone. Indeed, even if one substitutes homologues of CGRP as stated by the Examiner, the combination does not teach or suggest the present invention. Moreover, as previously submitted, '978 patent and the '478 patent are directed to the use of CGRP to ameliorate inflammatory conditions by inhibiting the release of the proinflammatory cytokines, IL-1, or &-1 and 1L-2, from immune cells such as macrophages and lymphocytes. The use of CGRP is disclosed by these patents as being useful for the treatment of a wide variety of diseases, of which asthma is only one.

In contrast to applicants' assertion that Cadieux et al. teach a method of using CGRP to inhibit ovalbumin allergen-induced AHR. Applicants are directed to the rejection discussed supra.

In contrast to applicants' argument that the '978 patent and the '478 patent do not teach AHR (page 18), this rejection would have been rejected under 35 USC 102(b) had each of the '978 patent and the '478 patent teach the use of CGRP for inhibiting allergen induced AHR.

In contrast to applicants' assertion that asthma and AHR are not one in the same condition (page 19), the specification on page 12 discloses that allergen induced airway hyperresponsiveness is an allergic inflammation of the airway characterized by an antigen driven IgE response, and Th2 type immune response (see page 12, first paragraph, in particular) and associated with inflammation (page 12, line 27, in particular). As evidence by the teachings of whitehead et al that asthma is a chronic inflammatory disease of the airway characterized by reversible airway obstruction, airway hyperactivity and infiltration of eosinophils in the lungs is a fundamental trait of inflammatory response in allergic asthma (see page L32, col. 1, in particular). The '478 patent teaches a method of treating asthma which is a chronic airway inflammatory disease by administering human CGRP (see col. 7, line 32-34, in particular). The '978 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness due to constriction, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular).

11. Claims 1, 25 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) as evident by Beaupre et al (Thorax 36(10): 731-6, Oct 1981; PTO 892) in view of Suissa *et al* (of record, Ann Intern Med 126(3): 177-83, Feb 1997; PTO 892).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention as recited in claim 25 differs from the teachings of the reference only that the agent reduces the airway hyperresponsiveness of the mammal such that the FEV1 value of said mammal is improved by at least about 5%.

The claimed invention as recited in claim 27 differs from the teachings of the reference only that the agent is a leukotriene modifiers such as receptor antagonist and β-agonists (along or short acting).

Suissa *et al* teach a combination of leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular). Suissa *et al* teach patients with mild-to-moderate asthma have a decrease in forced expiratory volume in 1 s (FEV1) which at least 55% of the predicted value and these patients have reduced airway hyperresponsiveness. The reference leukotriene receptor antagonist zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist or beta agonist as taught by Suissa *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Cadieux *et al* for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Suissa *et al* teach any combination of leukotriene receptor antagonist and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular) and zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5%

improvement (See entire document, abstract, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limiting the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with Suissa et al. does not teach or suggest the present invention. Suissa et al. only teach that a combination of leukotriene receptor antagonist and beta agonist is more effective than beta agonist alone in treating mild to moderate asthma. Such a teaching does not provide any teaching whatsoever regarding CGRP, and so one must look to Cadieux et al. to provide the teaching, motivation and expectation of success within the combination. Clearly, there is no motivation provided by Cadieux et al., which dissuades one from using CGRP to treat AHR during inflammatory conditions, to perform a method using any other agents for asthma, nor can the combination correct the deficiencies of Cadieux et al. or provide any more expectation of success at making and using the presently claimed invention as compared to Cadieux et al. alone (page 20).

In contrast to applicants' assertion that Cadieux et al. teach a method of using CGRP to inhibit ovalbumin allergen-induced AHR. Applicants are directed to the rejection discussed supra. Cadieux et al teach in vivo measurement of airway responses in guinea pigs sensitized with ovalbumin (page 236, animals and Sensitization procedures, in particular) and sensitivity to provoking agent such as acetylcholine or SP is measured with or without OA-sensitization and CGRP treatment (see page 236, col. 2, in particular). At highest dose of CGRP 6-M, CGRP inhibits OA-sensitized guinea pig bronchus ($7.2 \pm 4.5$) airway hyperresponsiveness to SP as compared to control ($20.3 \pm 1.5$) and is statistically significance ($p < 0.05$ versus control).

In response to applicants' there is no motivation or success in combining the references, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In this case the teachings of Suissa *et al* pertaining to a combination of leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular) and the teachings

of Cadieux et al indicating success of CGRP in inhibiting allergen induced AHR associated with inflammation of the airway in asthma would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Semaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144. Finally, there is no evidence that the method of used described in the instant claims would differ in an unexpected manner from those described in the references. In the absence of unexpected results, applicant's arguments were not found persuasive.

12. Claims 1 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) as evident by Beaupre et al (Thorax 36(10): 731-6, Oct 1981; PTO 892) in view of Drazen *et al* (of record, Am J Respir Crit Care Med 157(2): S233-7, June 1998; PTO 892) or Abraham *et al* (of record, Pulm Pharmacol 11(4): 271-6, June 1998; PTO 892) or Abdelaziz *et al* (Eur Respir J 10(4): 851-7; April 1997; PTO 892) or Barnes *et al* (of record, Eur Respir J 7(3): 579-91, March 1994; PTO 892) or Hoshino *et al* (of record, Allergy 52(8): 814-20, Aug 1997; PTO 892).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention as recited in claim 27 differs from the teachings of the reference only that the method wherein the agent is administered to a mammal in conjunction with another agent selected from the group consisting of β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, sodium cromoglycate, nedocrimal and theophylline.

Drazen *et al* teach leukotriene receptor antagonist such as (cysteinyl leukotriene (cysLT) and zafirlukast and 5-lipoxygenase (5-LO) inhibitor such as zileuton are safe and effective asthma treatment that improve pulmonary function and reduce airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular).

Abraham *et al* teach agents such as cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride and the combination gives better protection against post-

antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular).

Abdelaziz *et al* teach agent such as nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular).

Barnes *et al* teach agent such as theophylline for treatment of asthma and is widely use as a bronchodilator that has anti-inflammatory activities such as inhibiting cytokines synthesis and release, as well as airway hyperresponsiveness (See abstract, in particular).

Hoshino *et al* teach an agent such as Ketotifen, which is an antihistamine. Ketotifen is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil sodium as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* with the Calcitonin Gene-related peptide (CGRP) for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Drazen *et al* teach that any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach that nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach that theophylline is useful as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach that antihistamine is

beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with any of the above-identified secondary references does not teach or suggest the present invention. These references only provide a teaching of various compounds that might be useful to treat asthma or inflammation. None of the references provides any teaching whatsoever regarding CGRP, and so one must look to Cadieux et al. to provide the teaching, motivation and expectation of success within the combination. Clearly, there is no motivation provided by Cadieux et al., which dissuades one from using CGRP to treat AHR during inflammatory conditions, to perform a method using any other agents for asthma, nor can the combination correct the deficiencies of Cadieux et al. or provide any more expectation of success at making and using the presently claimed invention as compared to Cadieux et al. alone.

In response, the teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention as recited in claim 27 differs from the teachings of the reference only that the method wherein the agent is administered to a mammal in conjunction with another agent selected from the group consisting of β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, sodium cromoglycate, nedocrimal and theophylline.

Drazen *et al* teach leukotriene receptor antagonist such as (cysteinyl leukotriene (cysLT) and zafirlukast and 5-lipoxygenase (5-LO) inhibitor such as zileuton are safe and effective asthma treatment that improve pulmonary function and reduce airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular).

Abraham *et al* teach agents such as cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride and the combination gives better protection against post-

antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular).

Abdelaziz *et al* teach agent such as nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular).

Barnes *et al* teach agent such as theophylline for treatment of asthma and is widely use as a bronchodilator that has anti-inflammatory activities such as inhibiting cytokines synthesis and release, as well as airway hyperresponsiveness (See abstract, in particular).

Hoshino *et al* teach an agent such as Ketotifen, which is an antihistamine. Ketotifen is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil sodium as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* with the Calcitonin Gene-related peptide (CGRP) for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Drazen *et al* teach that any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach that nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach that theophylline is useful as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach that antihistamine is

beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

13. Claims 1, 28 and 39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) as evident by Beaupre et al (Thorax 36(10): 731-6, Oct 1981; PTO 892) in view of WO 98/03534 publication (January 1998; PTO 1449).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention in claim 28 differs from the teachings of the reference only that the agent is administered to said mammal in conjunction with a CGRP receptor activity modified protein (RAMP).

The claimed invention as recited in claim 39 differs from the teachings of the reference only that the agent is a fragment of CGRP that binds to and activates a CGRP receptor.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that the agent is a CGRP analog that binds to and activates a CGRP receptor.

The WO 98/03543 publication teaches various calcitonin gene-related peptide agonist such as CGRP-RCF analog and fragment thereof that binds to the CGRP receptor and retains essentially the same biological function as a human CGRP-polypeptide (See page 22, line 27, page 46, agonists and antagonists, in particular) for treating allergies (abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the Calcitonin Gene-related peptide (CGRP) as taught by Cadieux *et al* with the CGRP receptor activity modifying protein such as analog CGRP-RCF or

peptide fragment thereof as taught by the WO 98/03543 for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/03543 publication teaches the reference CGRP analog is useful for treating asthma and allergies (See abstract, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

Applicants' arguments filed 10/25/04 have been fully considered but are not found persuasive.

Applicants' position is that WO 98/03534 teach that CGRP-RCF is a CGRP receptor component factor, a 148 amino acid peptide which confers CGRP responsiveness to a CGRP receptor expressed by oocytes, apparently by allowing expression of the receptor. CGRP-RCF is not CGRP or an agonist or antagonist thereof. Page 16, lines 14-20 of WO 98/03534 teach that the receptor component factor refer to molecules other than CGRP receptor ligands or CGRP receptors. WO 98/03534 teach that CGRP-RCF might be useful to treat large number of virtually unrelated diseases. WO 98/03534 does not teach or suggest the use of CGRP or any compound to inhibit allergen-induced AHR and can not remedy the deficiencies of Cadieux et al. as discussed above, nor is there any motivation or expectation of success provided by the combination, because even with WO 98/03534, Cadieux et al dissuades one from using CGRP to treat AHR during inflammatory conditions.

In contrast to applicants' assertion that Cadieux et al dissuades one from using CGRP to treat AHR during inflammatory conditions, Cadieux et al teach CGRP to treat allergen such as ovalbumin sensitized AHR, and CGRP is markedly attenuated in inflammatory conditions (see page 242, col. 1, last paragraph, in particular). The reference ovalbumin and GCRP are the same ovalbumin and GCRP used by applicants.

In response to applicants' argument that CGRP-RCF of WO 98/03534 is not CGRP or an agonist or antagonist thereof, the WO 98/03543 publication teaches various calcitonin gene-related peptide agonist such as CGRP-RCF analog and fragment thereof that binds to the CGRP receptor and retains essentially the same biological function as a human CGRP-polypeptide (See

page 22, line 27, page 46, agonists and antagonists, in particular) for treating allergies (abstract, in particular). The claimed CGRP receptor activity modified protein (RAMP), and CGRP analog appear to be the same calcitonin gene-related peptide agonist such as CGRP-RCF analog and fragment thereof that binds to the CGRP receptor as taught by the WO 98/03543 publication in the absence of amino acid sequence. Since the Patent Office does not have the facilities for examining and comparing the CGRP receptor activity modified protein (RAMP), and CGRP analog of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the CGRP receptor activity modified protein (RAMP), and CGRP analog in the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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